Annals of Clinical and Analytical Medicine
Original Research

Relationship between respiratory problems and vitamin D levels in very low birth weight infants

Vitamin D levels and respiratory problems in preterm infants

Handan Hakyemez Toptan, Nilgun Karadag, Sevilay Topcuoglu, Emre Dincer, Abdulhamit Tuten, Selahattin Akar, Tulin Gokmen Yildirim, Elif Ozalkaya, Guner Karatekin, Fahri Ovali
Department of Neonatology, University of Health Sciences, Zeynep Kamil Maternity and Children's Disease Health Training and Research Center, Istanbul, Turkey

Abstract
Aim: The impact of vitamin D on the developing lungs and respiratory diseases in early life is increasingly attracting the attention of neonatologists. This study aimed to investigate the association between vitamin D [25 (OHD)] levels and respiratory problems in blood in infants with very low birth weight (VLBW).
Material and Methods: Sixty-six infants with VLBW were divided into two groups: those with a vitamin D level less than 20 ng/mL (Group 1) and infants with a vitamin D level equal to or greater than 20 ng/mL (Group 2). Infants' demographic data such as birth weight, gender, maternal age, gestational week, mode of delivery, and durations of mechanical ventilation, and length of stay in the hospital, mortality status, and BPD status were recorded.
Results: The median birth weight was 995.00 (min-max: 565-1500) g. The median gestational age was 28 (23-32) weeks and the median maternal age was 32 (21-46) years. All infants (n=66;100%) developed respiratory distress syndrome. A significant relationship was found between the severity of respiratory distress syndrome (RDS) and vitamin D deficiency in infants with VLBW ($r = 0.898$, $p = 0.001$). There was a significant correlation between the duration of hospitalization and 25 (OH) D levels within the first 24 hours ($p = 0.001$).
Discussion: Low 25 (OH) D levels in infants with VLBW were correlated with early-onset sepsis, severity of RDS, and duration of hospitalization. There was no significant correlation between vitamin D levels and PDA and BPD.

Keywords
25-hydroxy D Vitamin, Respiratory Distress Syndrome, Bronchopulmonary Dysplasia, Very Low Birth Weight

DOI: 10.4328/ACAM.21727 Received: 2023-04-14 Accepted: 2023-05-17 Published Online: 2023-05-30 Printed: 2023-07-01 Ann Clin Anal Med 2023;14(7):655-659
Corresponding Author: Handan Hakyemez Toptan, Department of Neonatology, University of Health Sciences, Zeynep Kamil Maternity and Children's Disease Health Training and Research Center, 34668, Üsküdar, Istanbul, Turkey.
E-mail: mdhandanhakyemez@gmail.com P: +90 532 318 46 56
Corresponding Author ORCID ID: https://orcid.org/0000-0002-6966-8514
This study was approved by the Ethics Committee of Zeynep Kamil Maternity and Children Training and Research Hospital (Date: 2016-11-25, No: 158)

Introduction

Vitamin D (25 [OH] D) is a steroid hormone, which functions primarily in the development of a healthy skeleton and in the regulation and maintenance of body levels of calcium levels [1]. The importance of 25 (OH) D in newborns has been increasingly better understood in the last few years [2]. Furthermore, vitamin D seems to play a crucial role in the regulation of lung development in the fetus, lung maturation and cellular growth [3]. Therefore, the impact of 25 (OH) D on developing neonatal lungs and respiratory diseases in early life is increasingly attracting the attention of neonatologists.

Maternal 25 (OH) D deficiency increases the risk of developing gestational diabetes mellitus, preeclampsia, intrauterine growth restriction and premature delivery [4]. These, in turn, trigger preterm delivery and preterm infants are at a greater risk of developing vitamin D deficiency. Vitamin D levels of the infant reflect the maternal levels. Since placental transfer is the primary source of vitamin D for the developing fetus, this means that maternal 25 (OH) D deficiency reflects vitamin D deficiency in a newborn [5]. Vitamin D deficiency has been correlated with various respiratory problems, including neonatal sepsis and respiratory system infections [6]. Studies have associated low 25OHD levels at birth with subsequent respiratory infections, such as respiratory syncytial virus [7]. There are also studies reporting that the prevalence of asthma is higher among preterm infants with low levels of 25OHD [8].

Very low birth weight (VLBW) infants are defined as infants born with a birth weight < 1500 g. These infants tend to develop several diseases, including respiratory problems. The majority of VLBW infants have respiratory distress syndrome. Bronchopulmonary dysplasia (BPD) was defined for the first time in 1967 by Northway in premature infants with respiratory distress syndrome (RDS) after prolonged ventilator support [9]. Some studies have reported that BPD remains the most common long-term complication of VLBW despite the use of minimally invasive strategies of respiratory support, prenatal steroids, and exogenous surfactants [10]. However, whether vitamin D deficiency is associated with BPD in VLBW infants is controversial and its potential contribution to BPD is not clear [11]. This study aimed to investigate the association between vitamin D [25 (OHD)] levels in the blood and respiratory problems in infants with VLBW.

Material and Methods

This study was designed as a prospective cross-sectional study. In total, the study included 66 infants with VLBW in a range of 565 and 1500 g who were followed-up in our neonatal intensive care unit (NICU) between 2016 and 2017. Infants receiving vitamin D before enrollment, those with congenital anomalies and infants with a history of maternal immunosuppressant therapy in the antenatal period were excluded from the study. Serum 25 (OH) D levels were measured on the postnatal 1st day, 28th day and 36th gestational week. The infants were divided into two groups: those with a vitamin D level less than 20 ng/mL (Group 1) and those with a vitamin D level equal to or greater than 20 ng/mL (Group 2).

Infants' demographic data such as birth weight, gender, maternal age, gestational week, mode of delivery, durations of mechanical ventilation, and length of stay in the hospital, mortality status, BPD status, surfactant use, number of times of receiving surfactant, antenatal steroids use, sepsis, pneumonia, oligohydramnios, 1st and 5th minutes Apgar scores, and CPAP status were recorded. In addition, the presence of oligohydramnios and preeclampsia was also recorded.

All infants included in the study received surfactant therapy. In infants in whom extubation could not be achieved immediately, synchronized intermittent mandatory ventilation (SIMV) was the primary mode of ventilation, providing a tidal volume with inspiratory time of 0.35 to 0.38 seconds, respiratory rates of 40 to 60 breaths/minute, and a positive end-expiratory pressure (PEEP) of 5-6 cm H2O. When a PIP of 15 cmH2O, PEEP of 4 -5 cmH2O, respiratory rate (RR) of 15 per minute and a FiO2 value ≤30% were obtained, patients were extubated to receive nasal CPAP.

The presence of patent ductus arteriosus (PDA) was evaluated through echocardiography in all infants included in the study on the 3rd day of life. If hemodynamically significant PDA was diagnosed, ibuprofen was given as pharmacologic treatment.

The associations between the levels of 25 (OH) D and respiratory disorders, including BPD, surfactant requirement, cPAP status, PDA status, length of hospital stay and mortality were investigated.

Blood samples of all patients were collected at the time of admission, on the 28th day and in the 36th gestational week during routine blood sampling. Plasmas of the blood samples were separated and kept at −80 °C until analysis. A High-Performance Liquid Chromatography (HPLC) System (Shimadzu LC-20AT model) was used to determine the levels of 25 (OH)D.

Ethical Considerations

Ethics Committee approval for the study was obtained from the local ethics committe of the Zeynep Kamil Maternity and Children Training and Research Hospital (Date: 2016-11-25, No: 158). Written informed consent was taken from the parents before the participation of their neonates in the study. The study was performed in accordance with the Declaration of Helsinki revised in 2013.

Statistical Analysis

Data obtained in this study were statistically analyzed using the SPSS version 21.0 (SPSS, Statistical Package for Social Sciences, IBM Inc., Armonk, USA). The normality of the variables was tested using the Kolmogorov-Smirnov method and expressed as a mean±standard deviation or median (IQR) as appropriate. Qualitative variables are expressed as percentages and frequencies, normally distributed continuous variables as means (standard deviations, SD) and non-normally distributed variables as medians (interquartile range [IQR] p25-p75). Pearson's correlation was used to evaluate the correlations between 25 OH vitamin D and other variables. The Chi-square test was performed for categorical variables. P- values <0.05 were considered statistically significant.

Ethical Approval

Ethics Committee approval for the study was obtained.

Results

This study included a total of 66 infants followed-up and treated in our NICU. The median birth weight was 995.00 (min-

max: 565-1500) g. The median gestational age was 28 (23-32) weeks and the median maternal age was 32 (21-46) years. Of all infants, 30 (45.45%) were male and 36 (54.55%) were female. Table 1 shows antenatal and demographic data of the infants.

The median 25 (OH) D level on the 1st day was 4.95 (3.90-10.53) ng/ml, and the median 25 (OH) D on the 26th day or at discharge was 15.5 (7.5-37.8) ng/ml. The distribution of patients according to 25 (OH) D is shown in Figure 1.

There was no significant difference between infants with 25 (OH) D <20 and ≥20 ng/mL between the two measurement times (p=0.083). All infants (n=66;100%) developed respiratory distress syndrome. Sixteen (24.24%) developed BPD, while 24 (36.36%) infants developed PDA and 20 (30.30%) developed pneumonia. Preeclampsia was observed in 19 (28.79%) and oligohydramnios in 6 (9.09%) mothers. Early sepsis was observed in 23 (34.85%) infants and late sepsis in 28 (42.42%) infants. Surfactants were required in 54 (81.82%) patients and steroids in 32 (48.48%) patients. The median duration of mechanical ventilation was 2 (0-8.50) days. The median duration of transit to enteral feeding was 14.50 (8.0-22.25) days. The median duration of hospitalization was 41.50 (26.5-68.0) days. Mortality occurred in 11 (16.67%) infants (Figure 2).

In the correlation analysis, a significant correlation was found between vitamin D deficiency and the severity of RDS in infants with VLBW (r = 0.898, p = 0.001). There was a significant correlation between low 25 (OH) D levels (<20 ng/mL) measured on the first day and sepsis (r=-0.557, p=0.003). However, there was no statistically significant correlation between low 25 (OH) D levels (<20 ng/mL) measured on the 28th day or at discharge and late sepsis (r=0.97, p=.094). No significant relationship was observed between BPD and 25(OH) D levels (p>0.05). No statistically significant correlation was observed between low levels of 25 (OH) D (<20 ng/mL) measured on the first day and PDA (p=0.887). Similarly, no statistically significant correlation was observed between low 25 (OH) D levels (<20 ng/mL) measured on the 28th day and PDA (p=0.615). A significant correlation was found between the duration of hospitalization and the levels of 25 (OH) D in the first 24 hours (p = 0.001). No correlation was observed between 25 (OH) D levels in the first 24 hours and mortality (r = 0.492, p = 0.931).

Table 1. Antenatal and demographic features of the patients.

Antenatal and demographic findings	
Female/male infants (n, %)	45.5/54.5% (30/36)
Median gestational week (IQR)	28 (23-32)
Median Birth weight (IQR)	995 (565-1500) g
Median value of 25 (OH) D value at the 1st day (IQR)	4.95 (3.90-10.53) ng/mL
Median value of 25 (OH) D value at 28.day or at discharge (IQR)	15.5 (7.5-37.38) ng/mL
Median duration of mechanical ventilation (IQR)	2.0 (0-8.0) days
Median duration to transit to enteral feeding	14.50 (8.0-22.25) days
Median duration of hospitalization	41.50 (26.5-68.0) days

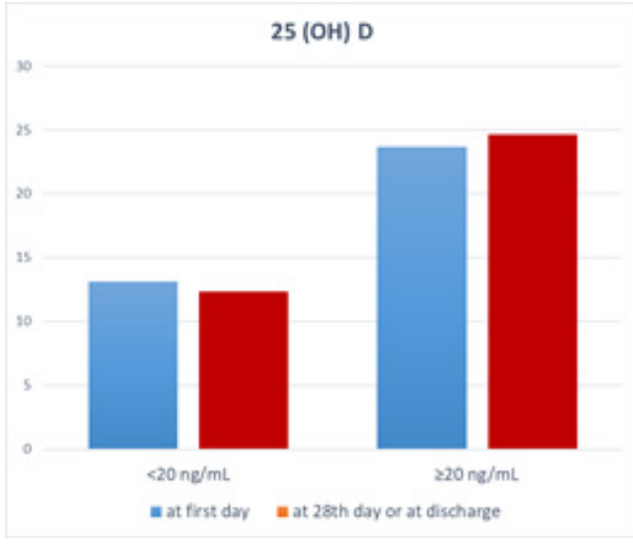

Figure 1. Distribution of 25 (OH) D values.

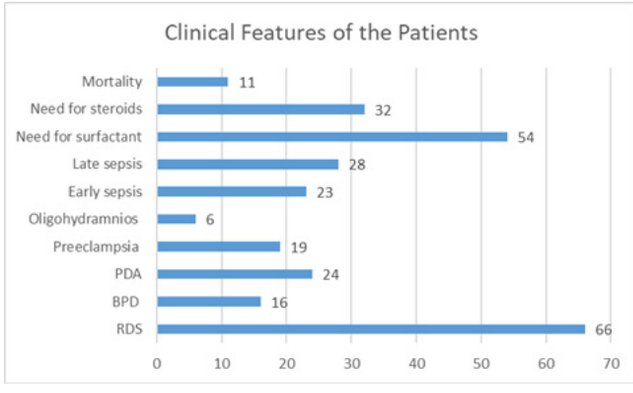

Figure 2. Clinical features of the patients.

Discussion

There is increasing global interest regarding the role of vitamin D in health and disease. Vitamin D is known to play a role in human pulmonary function [12]. Studies have shown that patients with lung diseases often have low Vitamin D serum levels. Epidemiological data indicate that low levels of serum Vitamin D are associated with impaired pulmonary function, increased incidence of inflammatory, infectious or neoplastic diseases [13]. Vitamin D deficiency in blood has also been associated with increased incidence of respiratory tract infections during infancy [14]. Wide biological effects of Vitamin D, suggest that the deficiency of vitamin D during the fetal and neonatal periods may have long-lasting health consequences [15]. It has also been shown that low blood levels of Vitamin D are associated with an increased risk of respiratory problems [16]. In the present study, we evaluated the effects of Vitamin D deficiency on respiratory problems in low-birth-weight infants.

Neonatal RDS is a common cause of respiratory distress in newborns that present within hours after birth. RDS primarily affects preterm infants [17]. Critical factors playing a role in the pathogenesis of neonatal RDS include surfactant deficiency and pulmonary immaturity. In the present study, 54/66 infants required surfactant therapy. In our study, all VLBW infants had respiratory distress syndrome. In addition, a significant relationship was found between the severity of RDS and deficiency of vitamin D in infants with VLBW (r = 0.898, p = 0.001). Dogan et al. showed that vitamin D deficiency was an independent factor for the development of RDS in premature infants [18].

Neonatal sepsis is defined as a systemic condition originating

from bacterial, viral or fungal causes and is associated with hemodynamic changes and clinical findings causing severe morbidity and mortality [19]. While early-onset sepsis describes cases presenting manifestations within the first 72 hours of life, late-onset sepsis describes cases diagnosed after the first seven days [20]. Low vitamin D levels that are generally common in the neonatal population have been found to be significantly higher in neonates with sepsis [21]. In the present study, there was a significant correlation between low 25 (OH) D levels (<20 ng/mL) measured on the first day and sepsis (r=-0.557, p=0.003). However, there was no statistically significant correlation between low 25 (OH) D levels (<20 ng/mL) measured on the 28th day or at discharge and late sepsis (r=0.97, p=.094). We think that the difference in late sepsis may be due to the effect of surfactant supplementation, which was initiated from the first day of life in our study.

BPD is a chronic pulmonary disorder that primarily affects preterm infants. The new BPD definition differs from the first and is characterized by pulmonary vascular dysplasia or hypoplasia and alveolar simplification rather than scarring and fibrosis of the lungs [22]. Potential contribution of Vitamin D deficiency to BPD is unknown. Joung et al found no correlation between 25(OH) D levels and the development of BPD [11]. In our study also no significant relationship was observed between BPD and the levels of 25(OH) D (p>0.05). Furthermore, in a meta-analysis and systematic review, including eight studies, the authors concluded that the vitamin D levels at the time of birth, reflecting maternal and fetal vitamin D status during pregnancy, was significantly correlated with the incidence of BPD. However, no information was given about the later measurements of vitamin D levels [23].

A patent ductus arteriosus occurs commonly in preterm infants, especially in those with respiratory distress syndrome. In our study, PDA occurred in 36.36% (24/66) of VLBW infants. Studies have proposed that severe RDS justifies a controlled trial of very early closure of the PDA in the very low-birth-weight infant with severe RDS [24]. In a study by Kim et al., PDA occurred in 48.4% of VLBW infants [25]. In our study, PDA was observed in 24 (36.4%) of VLBW infants. We could not find a significant difference between Vitamin D deficiency and PDA.

In the present study, a significant correlation was observed between hospitalization duration and the levels of 25 (OH) D in the first 24 hours (p = 0.001). No correlation was observed between 25 (OH) D levels in the first 24 hours and mortality (r = 0.492, p = 0.931).

Study Limitations

The main limitations of this study include its single-center design and relatively small number of patients. In addition, a control group with term infants could be created. Finally, we could not compare maternal and neonatal vitamin D levels. However, given the limited number of existing data in the literature and the need for further studies, we believe that our results will guide for future more comprehensive studies.

Conclusion

The results of this study revealed that low 25 (OH) D levels in infants with VLBW were correlated with early-onset sepsis, severity of RDS, and duration of hospitalization. There was no statistically significant correlation between the levels of vitamin D and BPD and PDA. However, there is a need for further comprehensive studies with larger series to better enlighten these correlations.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

Funding: *None*

Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

References

1. Jäpelt RB, Jakobsen J. Vitamin D in plants: a review of occurrence, analysis, and biosynthesis. Front Plant Sci. 2013;13(4):136.

2. Christesen HT, Elvander C, Lamont RF, Jørgensen JS. The impact of vitamin D in pregnancy on extraskeletal health in children: a systematic review. Acta Obstet Gynecol Scand. 2012;91(12):1368-80.

3. Yang Y, Feng Y, Chen X, Mao XN, Zhang JH, Zhao L, et al. Is there a potential link between vitamin D and pulmonary morbidities in preterm infants? J Chin Med Assoc. 2018;81(5):482-6.

4. Wei SQ. Vitamin D and pregnancy outcomes. Curr Opin Obstet Gynecol. 2014;26(3):438-47.

5. Al-Beltagi M, Rowiesha M, Elmashad A, Elrifaey SM, Elhorany H, Koura HG. Vitamin D status in preterm neonates and the effects of its supplementation on respiratory distress syndrome. Pediatr Pulmonol. 2020;55(1):108-15.

6. Terek D, Ozcan G, Ergin F, Koroglu Altun O, Yalaz M, Akisu M, et al. Vitamin D Deficiency in Premature Infants and Its Effects on Neonatal Prognosis. J Pediatr Res. 2018;5(1):37-40.

7. Belderbos ME, Houben ML, Wilbrink B, Lentjes E, Bloemen EM, Kimpen JL, et al. Cord blood vitamin D deficiency is associated with respiratory syncytial virus bronchiolitis. Pediatrics. 2011;127(6):e1513-20.

8. Brehm JM, Acosta-Pérez E, Klei L, Roeder K, Barmada M, Boutaoui N, et al. Vitamin D insufficiency and severe asthma exacerbations in Puerto Rican children. Am J Respir Crit Care Med. 2012;186(2):140–-6.

9. McEvoy CT, Aschner JL. The Natural History of Bronchopulmonary Dysplasia: The Case for Primary Prevention. Clin Perinatol. 2015;42(4):911-31.

10. Mahmoud RA, Roehr CC, Schmalisch G. Current methods of non-invasive ventilatory support for neonates. Paediatr Respir Rev. 2011;12(3):196-205.

11. Joung KE, Burris HH, Van Marter LJ, McElrath TF, Michael Z, Tabatabai P, et al. Vitamin D and bronchopulmonary dysplasia in preterm infants. J Perinatol. 2016;36(10):878-82.

12. Black PN, Scragg R. Relationship between serum 25-hydroxyvitamin d and pulmonary function in the third national health and nutrition examination survey. Chest. 2005;128(6):3792-8.

13. Herr C, Greulich T, Koczulla RA, Meyer S, Zakharkina T, Branscheidt M, et al. The role of vitamin D in pulmonary disease: COPD, asthma, infection, and cancer. Respir Res. 2011;12(1):31.

14. Panda M, McIntosh J, Chaudhari T, Kent AL. Do Maternal Vitamin D Levels Influence Vitamin D Levels in Preterm Neonates? Int J Pediatr. 2019;2019:8613414.

15. Holick MF. High prevalence of vitamin D inadequacy and implications for health. Mayo Clin Proc. 2006;81(3):353-73.

16. Camargo CA Jr, Ingham T, Wickens K, Thadhani R, Silvers KM, Epton MJ, et al. Cord-blood 25-hydroxyvitamin D levels and risk of respiratory infection, wheezing, and asthma. Pediatrics. 2011;127(1):e180-7.

17. Yadav S, Lee B, Kamity R. Neonatal Respiratory Distress Syndrome. Treasure Island (FL): StatPearls Publishing; 2021.

18. Dogan P, Ozkan H, Koksal N, Bagci O, Varal IG. Vitamin D deficiency and its effect on respiratory distress syndrome in premature infants: results from a prospective study in a tertiary care centre. Afr Health Sci. 2020;20(1):437-43.

19. Ozmeral Odabasi I, Bulbul A. Neonatal Sepsis. Med Bull Sisli Etfal Hosp. 2020;54(2):142-58.

20. Dong Y, Speer CP. Late-onset neonatal sepsis: recent developments. Arch Dis Child Fetal Neonatal Ed. 2015;100(3):F257-63.

21. Workneh Bitew Z, Worku T, Alemu A. Effects of vitamin D on neonatal sepsis: A systematic review and meta-analysis. Food Sci Nutr. 2020;9(1):375-88.

22. Xu YP. Bronchopulmonary Dysplasia in Preterm Infants Born at Less Than 32 Weeks Gestation. Glob Pediatr Health. 2016; DOI: 10.1177/2333794X16668773.

23. Park HW, Lim G, Park YM, Chang M, Son JS, Lee R. Association between vitamin D level and bronchopulmonary dysplasia: A systematic review and meta-analysis. PLoS One. 2020;15(7):e0235332.

24. Nemri AM. Patent ductus arteriosus in preterm infant: Basic pathology and when to treat. Sudan J Paediatr. 2014;14(1):25-30.
25. Kim I, Kim SS, Song JI, Yoon SH, Park GY, Lee YW. Association between vitamin D level at birth and respiratory morbidities in very-low-birth-weight infants. Korean J Pediatr. 2019;62(5):166-72.

How to cite this article:
Handan Hakyemez Toptan, Nilgun Karadag, Sevilay Topcuoglu, Emre Dincer, Abdulhamit Tuten, Selahattin Akar, Tulin Gokmen Yildirim, Elif Ozalkaya, Guner Karatekin, Fahri Ovali. *Relationship between respiratory problems and vitamin D levels in very low birth weight infants. Ann Clin Anal Med 2023;14(7):655-659*

This study was approved by the Ethics Committee of Zeynep Kamil Maternity and Children Training and Research Hospital (Date: 2016-11-25, No: 158)